

**REMARKS**

Claims 22 and 85 are pending.

In response to the Amendment submitted July 13, 2004, the objections to the specification and the rejections under 35 U.S.C. §101 for alleged lack of utility and under 35 U.S.C. §112 for alleged new matter/lack of written description have all been withdrawn.

The sole rejection pending is based on the Examiner's contention that the specification does not enable the claimed antibodies. For reasons set forth in detail below, it is respectfully requested that the rejection be withdrawn and that the claims be deemed allowable.

Applicants also request that the Examiner indicate whether the Information Disclosure Statement and PTO-1449 form mailed by Applicants on December 30, 2003 (together with cited references) has now been made of record. A copy of the postcard indicating that this Information Disclosure Statement was received by the Patent Office on January 2, 2004 is attached.

**1. The Claims Are Enabled**

Claims 22 and 85 are rejected under the first paragraph of 35 U.S.C. § 112 for lack of enablement. The Examiner has not been convinced by Applicants' arguments for the following reasons.

First, the Examiner is not persuaded by Applicants' argument that "the specification teaches that an antibody could be used to detect the expression of Old-35 toward determining whether a cell is senescent, terminally differentiated, or growth arrested" because, according to the Examiner, "there is no evidence of record that aberrations of cellular senescence, such as that found in a disorder such as cancer, are correlative with the expression of the OLD-35

protein.” The Examiner concludes:

It would require further experimentation by the skilled artisan to characterize the regulation of OLD-35 protein expression during the disease process as well as during chemotherapy to ascertain whether monitoring the expression of the OLD-35 protein is indicative of the effectiveness of the chemotherapy, for example.

Second, the Examiner does not agree with Applicants that mRNA levels are “validly correlated with protein expression.”

Third, the Examiner contends that there is no teaching, either in the specification or in Leszczyniecka et al., 2002, "Identification and cloning of human polynucleotide phosphorylase, *hPNPase*<sup>old-35</sup>, in the context of terminal differentiation and cellular senescence," Proc. Natl. Acad. Sci. 99:16636-16641 ("Leszczyniecka"; attached as Exhibit B to the Amendment filed July 13, 2004), that there is “any correlation between an altered expression level of OLD-35 protein and a specific disease state such as cancer, for example.”

Fourth, the Examiner states that Applicants “did not address the art of Fu et al., Powell et al., Vallejo et al., Lewin and Jang et al.” in view of which, according to the Examiner, “the skilled artisan cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to the complex homeostatic factors controlling translational and post-translational modification.”

Finally, the Examiner concludes:

the skilled artisan would not know how to use antibodies that bind the OLD-35 protein because Applicant has not provided any objective evidence of OLD-35 protein expression (ELISA or Western blot) correlated with a specific disease state or condition such that detection of OLD-35 would be indicative of disease progression or regression.

Applicants respectfully request that the Examiner reconsider the basis for his rejection for the following reasons.

**A. OLD-35 Can Be Used To Determine Whether A Cell is Senescent, Terminally Differentiated Or Growth Arrested Because the Specification Presents Data Showing a Correlation Between Old-35 mRNA Levels And These Conditions And Teaches That Measuring OLD-35 Protein Can Be Used As An Alternative To Measuring mRNA**

As to the first contention of the Examiner, Applicants respectfully disagree because they have indeed provided evidence that expression of Old-35 can be used to determine whether a cell is senescent, terminally differentiated, or growth arrested.

As pointed out in the response filed July 13, 2004, Figure 1 of the instant application shows that the level of Old-35 mRNA is much higher in senescent Progeria (premature ageing) cell lines (lanes 5 and 6) relative to young fibroblasts (lane 4). Likewise, Figure 2D demonstrates that treatment of melanoma cells with the differentiation-promoting agents interferon beta (IFN- $\beta$ ) and mezerein increases the level of Old-35 mRNA. The specification teaches that OLD-35 protein is an alternative to Old-35 mRNA as a means for measuring expression of the Old-35 gene (in the instant specification, for example, at page 20 lines 31-35 and at page 21 lines 3-6 and 11-15). Therefore, the skilled artisan would readily appreciate the utility of antibodies toward OLD-35 protein as a means of detecting differentiation in melanoma cells (a disease) or senescence (a condition) in fibroblasts.

Contrary to the Examiner's contention, a skilled artisan would *not* be required, in order to know how to use the invention, to do clinical studies to show a correlation between Old-

35 and regression of cancer during chemotherapy. Based on the specification's disclosure of a correlation between increased OLD-35 expression and senescence in progeria cells or differentiation of melanoma cells, the skilled artisan would appreciate how an antibody to OLD-35 could be used.

**B. Changes In Old-35 mRNA Correlate With Changes in OLD-35 Protein**

The specification expressly states that OLD-35 protein can be used as an alternative to Old-35 mRNA for detecting changes in Old-35 gene expression (in the instant specification, for example, at page 20 lines 31-35 and at page 21 lines 3-6 and 11-15). The Examiner has essentially questioned the credibility of this teaching, based on references such as Fu et al., Powell et al., Vallejo et al., Lewin and Lewin and Jang, in light of which the skilled artisan, according to the Examiner, would not anticipate a parallel between mRNA and protein expression patterns.

In support of the parallel correlation between Old-35 mRNA and OLD-35 protein levels, Applicants submit herewith a Declaration of Dr. Paul Fisher (the "Fisher Declaration") in which Dr. Fisher avers that "there is a clear correlation between an increase in Old-35 mRNA expression and a proportionate increase in OLD-35 protein levels within cells" (the Fisher Declaration, section 4A, last sentence). Dr. Fisher presents evidence of an antibody recognizing endogenous cellular OLD-35 protein. He demonstrates by presenting supporting data (EXHIBIT 2) that the increase in OLD-35 protein level as detected and measured by the anti-OLD-35 antibody occurs in cells treated with an agent that causes cells to undergo growth arrest and terminal differentiation. Thus Dr. Fisher establishes that detection of OLD-35 protein utilizing a

suitable antibody would be an effective means in determining the physiological condition of a cells with respect to growth arrest, differentiation, aging status or disease state (the Fisher Declaration, section 4C). Further, Dr. Fisher avers that the claimed antibodies (which are required to bind to a protein with amino acid sequence SEQ ID NO:42, which comprises amino acid residues 18-696 of the 783 amino acid-containing OLD-35 protein plus nine additional residues at the C-terminus not found in the native protein), would be expected to bind to native OLD-35 protein (because the additional residues constitute only approximately one percent of the entire sequence).

Therefore, because:

(1) the specification shows a correlation between an increase in OLD-35 protein and cellular senescence, inhibited growth, and differentiation;

(2) the specification teaches that OLD-35 protein levels can be used as an alternative to mRNA to measure *Old-35* gene expression;

(3) changes in OLD-35 protein levels are experimentally established as a valid surrogate for Old-35 mRNA in measuring gene expression; and

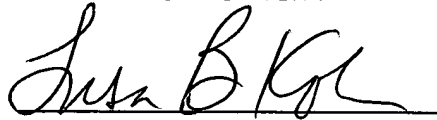
(4) the claimed antibodies, which are required to bind to a protein having the amino acid sequence of SEQ ID NO:42, would be expected to bind OLD-35 protein (the Fisher Declaration, section 4B); a skilled artisan would know how to use the claimed antibodies, so that the claims are enabled and the pending rejection should be withdrawn.

**2. CONCLUSION**

For the foregoing reasons, Applicants submit that the present application is in condition for allowance of Claims 22 and 85. A Notice of Allowance is therefore respectfully requested.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read "Lisa B. Kole", written over a horizontal line.

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